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Risk of Decompression Sickness in the Presence of Circulating Microbubbles

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Abstract:

In this study, we examined the association between microbubbles formed in the circulation from a free gas phase and symptoms of altitude decompression sickness (DCS). In a subgroup of 59 males of mean (S.D) age 31.2 (5.8) years who developed microbubbles during exposure to 26.59 kPa (4.3 psi) under simulated extra-vehicular activities (EVA), symptoms of DCS occurred in 24 (41%) individuals. Spencer grade I microbubbles occurred in 4 (7%), grade II in 9 (15%), grade III in 15 (25%), and grade IV in 31 (53%) of subjects. Survival analysis using Cox proportional hazards regression showed that individuals with >grade III CMB showed 2.46 times (95% confidence interval=1.26 to 5.34) higher risk of symptoms. This information is crucial for defining the risk of DCS for inflight Doppler monitoring under space EVA.

Altitude decompression sickness (DCS) occurs when there is acute reduction in ambient pressure. The symptoms of DCS are due to the formation of a free gas phase (in the form of gas microbubbles) in tissues during decompression. Musculo-skeletal pain of bends is the commonest form of DCS in altitude exposures. In the space flight environment, there is a risk of DCS when astronauts decompress from the normobaric shuttle pressure into the hypobaric space suit pressure (currently about 29.65 kPa [4.3 psi]) for extra-vehicular activities (EVA). This risk is counterbalanced by a judicious combination of prior denitrogenation and staged decompression (1).

Studies on DCS are limited by the duration of the test at reduced pressure. Since only a proportion of subjects tested develop symptoms, the information on DCS is generally incomplete or "censored". Many studies employ Doppler ultrasound monitoring of the precordial area for detecting circulating microbubbles (CMB). Although the association between

CMB and bends pain is not causal, CMB are frequently monitored during decompression.

In this paper, we examine the association between CMB and symptoms of DCS under simulated EVA profiles.

Methods:

The information on a subgroup of 59 males who developed CMB (out of 126 individuals) during various decompression profiles to 29.65 kPa in the hypobaric chamber were examined. The studies involved direct ascent, as well as staged decompression procedures. All the subjects breathed 100% oxygen at the final pressure while performing exercises simulating EVA for a period of three to six hours (1). They were monitored for CMB using the precordial Doppler technique, and graded on the Spencer scale of 0 to IV for severity (2). A 360-minute half-time tissue ratio (TR_{360}) was calculated to account for differences in prebreathe period and staged decompression events.

The distribution of individuals with and without symptoms was examined by using Kolmogorov-Smirnov test or likelihood ratio chi-square test, as appropriate. Univariate survival curves were described using product-limit method. Differences in survival curves were examined by using the Mantel-Cox test statistic (3). Multivariate analyses were carried out using Cox proportional hazards regression model (3,4) with variables such as age, body mass index (BMI), TR_{360}, time to detection of CMB and maximum grade of CMB as covariates. All results with P-values of 0.05 and below were considered as significant.

Results:

The mean (S.D.) age was 31.2 (5.8) years, BMI 23.7 (1.9), TR_{360} 1.72 (0.09), time to detection of CMB 81.4 (61.8) minutes, maximum CMB grade 3.24 (0.95), and time to symptoms 197.9 (104.6) minutes. Twenty-four individuals (41%) presented with symptoms of DCS. All symptoms were mild, joint pain ("bends") and no neurological or circulatory complications were reported. The distribution of individual characteristics by symptom status (present or absent) is given in Table 1.

The symptom-free survival rates for the group with various grades of CMB are given in Table 2.

The Mantel-Cox test for trend showed a significant difference (P=0.004) among the groups with various maximum CMB grades. It may also be seen from the Table that the cumulative survival rates reduced as the maximum grade of CMB was higher. Individuals with higher grades of CMB showed higher risk of symptoms.

Table 1. Individual Distribution By Symptom Status

	Present n=24	Absent n=35
Age (years)	33.3 (6.4)	29.8 (4.8)
BMI	23.5 (1.9)	23.8 (1.9)
TR_{360}	1.7 (0.1)	1.7 (0.1)
Time to CMB (min)	68.4 (57.5)	90.3 (63.9)
Maximum CMB grade*		
≤III	4 (17%)	24 (69%)
>III	20 (83%)	11 (31%)

Values are Mean (S.D.); BMI=Body Mass Index; CMB=Circulating Microbubbles; *P<0.05

Table2. Symptom-free Cumulative Survival Rates

CMB grades	n	DCS	Survival (S.D.)
I	4	2	0.33 (0.27)
II	9	0	1.00
III	15	2	0.87 (0.09)
IV	31	11	0.15 (0.12)

In order to examine this trend, we classified the individuals into two groups- those with maximum CMB grades ≤III and >III. Distribution by maximum CMB grade is given in Table 3.

Table 3. Individual Characters by Maximum Grade of CMB

	>III n=31	≤III n=28
Age (years)	32.2 (6.3)	30.1 (5.0)
BMI	23.7 (1.9)	23.7 (1.9)
TR_{360}	1.73 (0.07)	1.69 (0.11)
Time to CMB (min)	59.3 (51.9)	105.8 * (63.5)

Values are Mean (S.D.); *P<0.05

The risk of DCS in the presence of higher grades of microbubbles was examined by calculating the relative risk values (5). Cox proportional hazards regression was used to adjust for various other factors such as age, BMI, TR_{360} and time to detection of CMB. The results of this analysis are given in Table 4.

Table 4. Relative Risk of Symptoms of DCS

CMB	DCS Yes	DCS No	Crude RR	Adjusted RR+
Grade ≤III	4	24	1.00	1.00
>III	11	20	4.52* (1.76-11.61)	2.46* (1.26-5.34)

RR=Relative Risk; 95% confidence intervals in parentheses
*P<0.01
+Adjusted for age, BMI, TR360, and time to detection of CMB in the Cox proportional hazards regression model.

These results showed that individuals with greater than grade III CMB were at increased risk of symptoms.

Discussion:

Before examining the association between CMB and symptoms of altitude DCS, two important issues must be considered. They are:

* *cause and effect*
* *censoring of information*

Although microbubbles occur during decompression, their relationship to symptoms may not be causal. This is especially a problem in case of bends pain. The pain of bends is thought to be due to the formation of free gas microbubbles in extravascular tissues (2), as opposed to the intravascular circulating microbubbles detected by the precordial Doppler. However, this data could be used in a predictive manner to monitor the development of symptoms of DCS (6). This information is usually censored, so not amenable to traditional methods of analysis.

Survival analysis is useful under these circumstances. The distribution of survival times is divided into a certain number of intervals. For each interval, the proportion with symptoms (or any "event"), and the proportion that were lost or censored are obtained. Then the cumulative proportion of cases surviving through each interval is calculated. In the product-limit method, the cumulative proportion thus obtained is a maximum likelihood estimate (3,4).

Utilizing survival analysis we found that individuals with Spencer grade IV CMB showed 2.46 times higher risk of symptoms, compared to individuals with lower grades. This risk was unchanged, even after adjusting for the influence of other variables in the regression model.

There are several implications from these results. Neurological symptoms and other severe complications of DCS are main concerns under space EVAs. While ground-based studies indicate a 10% to 20% risk of minor DCS symptoms, no cases have been reported from space EVAs.

Several steps have been taken to examine this *"decompression anomaly"* in space. Our analysis showed increased risk of DCS with higher CMB grades during simulated EVA profiles. This finding would provide a strong case for inflight precordial Doppler monitoring of astronauts in the space suit during space EVA. Further, this finding would permit definition of a high risk group for DCS, based on the obtained information on CMB. A program for meeting these objectives is currently being developed at this Laboratory.

References:

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